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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/553,993 | 04/20/2000 | Kevin Gunderson | A-69235/DJB/RMS/DCF | 5906 |

7590 03/29/2005

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EXAMINER

FORMAN, BETTY J

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1634

DATE MAILED: 03/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/553,993

Applicant(s)

GUNDERSON ET AL.

Examiner

BJ Forman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 January 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 15-29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15-29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

Status of the Claims

1. This action is in response to papers filed 7 January 2005 in which claims 22 and 29 were amended. The amendments have been thoroughly reviewed and entered.

The previous rejections in the Office Action dated 14 May 2004 under 35 U.S.C. 112, first paragraph are withdrawn in view of the citations from the specification on pages 8-10. The previous rejections under 35 U.S.C. 112, second paragraph are withdrawn in view of the amendments. The previous rejections under 35 U.S.C. 103(a), not reiterated below, are withdrawn in view of the amendments and/or Applicant's comments regarding new matter. The previous rejections under obviousness-type double patenting are maintained.

Applicant's arguments have been thoroughly reviewed and are discussed below as they apply to the instant grounds for rejection. New grounds for rejection are discussed.

This action is made non-final to include the New Matter rejection detailed below.

Claims 15-29 are under prosecution.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 22-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

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relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In amendments filed 2 December 2002, new Claims 22-28 were added. Claim 22 is independent. Claims 23-28 depend from Claim 22. New Claim was added reciting "simultaneously detecting at least sixteen target nucleic acid sequences", "at least sixteen pairs of primers to a first portion of at least sixteen target sequences". Applicant did not point to any passage within the originally filed specification for the newly claimed 1) simultaneous detection; 2) sixteen primer pairs; 3) sixteen targets; or 4) the open ended and undefined range encompassed by the "at least" sixteen primer pairs or targets. The examiner performed a text search of the specification but no support for the new claim language was found. Therefore, the new claim language is deemed new matter.

MPEP 2163.06 notes "If NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE" (emphasis added).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

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matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 29, 15-17, 19-20, 22-24 and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Macevicz (U.S. Patent No. 6,280,935, filed 4 June 1998) in view of Ullman et al (U.S. Patent No. 5,185,243, issued 9 February 1993) and Collins (U.S. Patent No. 5,750,338, issued 12 May 1998).

Regarding Claim 29, Macevicz teaches a method of detecting a target nucleic acid sequence, said method comprising: hybridizing a first primer portion comprising an adapter sequence (ligation probe) to a target sequence; hybridizing a second primer to a second portion of said target sequence; ligating said first and second primer to form a modified primer; contacting said modified primer with an array comprising: a substrate with a surface comprising discrete sites and a population of microspheres comprising a first nucleic acid capture probe that hybridizes to said adapter sequence wherein said microspheres are distributed on said surface and detecting the presence of said target sequence (Column 34, lines 11-38). Macevicz does not teach that the first and second portions of the target sequences are non adjacent and extending either the first or second primer toward the other.

However, Ullman et al teach a similar method comprising: hybridizing a first primer portion to a target sequence; hybridizing a second primer to a second portion of said target sequence wherein the first and second target regions are not adjacent; extending one of the primer toward the other and ligating said first and second primer to form a modified primer and capturing the modified primer (Column 4, line 45-Column 6, line 5; and Column 9, line 59-Column 10, line 18) wherein the extension of non-adjacent primers eliminates the need to identify the diagnostic sequence thereby facilitating diagnostic detection and increasing the specificity and sensitivity of diagnostic detection (Column 4, lines 3-12).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the primers of Macevicz by designing primers that hybridize to

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non-adjacent target positions as taught by Ullman et al for the expected benefit of eliminating the need to identify the diagnostic sequence thereby facilitating diagnostic detection and further increasing the specificity and sensitivity of diagnostic detection as taught by Ullman et al (Column 4, lines 3-12).

Macevicz and Ullman do not teach the target is immobilized on a solid phase surface during hybridization between the first primer and target. However, target immobilization during a first hybridization step was well known in the art at the time the claimed invention was made as taught by Collins (e.g. Fig.6). Collins et al teach a similar method of target detection comprising a first step of hybridizing a first primer and a target, wherein the target is immobilized whereby the target immobilization facilitates removal of non-specific material from the sample and concentrates the target for detection and greater purification of detectable product (Column 5, lines 19-25). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the target immobilization of Collins et al to the target detection of Macevicz and Ullman for the expected benefit removal of non-specific material from the sample, concentration the target for detection and greater purification of detectable product as taught by Collins (Column 5, lines 19-25).

Regarding Claim 15, Macevicz teaches the method further comprising detecting a second target sequence (i.e. population of library members) thereby comprising hybridizing third and forth primers to first and second portions of the second target; contacting with said array and detecting the presence of said second target (Column 16, lines 12-67).

Regarding Claim 16, Macevicz teaches the method wherein the modified primer is amplified (Column 16, line 10-Column 19, line 49).

Regarding Claim 17, Macevicz discloses the method wherein the detecting is done by hybridizing a labeled probe (Column 24, lines 63-67). And Ullman et al teach their similar method wherein the detecting is done by hybridizing a labeled probe (Column 22, lines 9-42).

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Regarding Claim 19, Macevicz discloses the method wherein said discrete sites comprise wells (Column 32, lines 5-10).

Regarding Claim 20, Macevicz discloses the method wherein the detecting is done by hybridizing a labeled probe (Column 24, lines 63-67). And Ullman et al teach their similar method wherein the detecting is done by hybridizing a labeled probe (Column 22, lines 9-42).

Regarding Claim 22, Macevicz teaches a method of detecting a plurality of target nucleic acid sequences, (i.e. population of library members, Column 16, lines 12-67) said method comprising: hybridizing a first primer portion comprising an adapter sequence (ligation probe) to a target sequence; hybridizing a second primer to a second portion of said target sequence; ligating said first and second primer to form a modified primer; contacting said modified primer with an array comprising: a substrate with a surface comprising discrete sites and a population of microspheres comprising a first nucleic acid capture probe that hybridizes to said adapter sequence wherein said microspheres are distributed on said surface and detecting the presence of said target sequence (Column 34, lines 11-38). Macevicz does not teach that the first and second portions of the target sequences are non adjacent and extending either the first or second primer toward the other.

However, Ullman et al teach a similar method comprising: hybridizing a first primer portion to a target sequence; hybridizing a second primer to a second portion of said target sequence wherein the first and second target regions are not adjacent; extending one of the primer toward the other and ligating said first and second primer to form a modified primer and capturing the modified primer (Column 4, line 45-Column 6, line 5; and Column 9, line 59-Column 10, line 18) wherein the extension of non-adjacent primers eliminates the need to identify the diagnostic sequence thereby facilitating diagnostic detection and increasing the specificity and sensitivity of diagnostic detection (Column 4, lines 3-12).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the primers of Macevicz by designing primers that hybridize to

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non-adjacent target positions as taught by Ullman et al for the expected benefit of eliminating the need to identify the diagnostic sequence thereby facilitating diagnostic detection and further increasing the specificity and sensitivity of diagnostic detection as taught by Ullman et al (Column 4, lines 3-12).

Macevicz and Ullman do not teach the target is immobilized on a solid phase surface during hybridization between the first primer and target. However, target immobilization during a first hybridization step was well known in the art at the time the claimed invention was made as taught by Collins (e.g. Fig.6). Collins et al teach a similar method of target detection comprising a first step of hybridizing a first primer and a target, wherein the target is immobilized whereby the target immobilization facilitates removal of non-specific material from the sample and concentrates the target for detection and greater purification of detectable product (Column 5, lines 19-25). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the target immobilization of Collins et al to the target detection of Macevicz and Ullman for the expected benefit removal of non-specific material from the sample, concentration the target for detection and greater purification of detectable product as taught by Collins (Column 5, lines 19-25).

Regarding Claim 23, Macevicz teaches the method wherein the modified primer is amplified (Column 16, line 10-Column 19, line 49).

Regarding Claim 24, Macevicz discloses the method wherein the detecting is done by hybridizing a labeled probe (Column 24, lines 63-67). And Ullman et al teach their similar method wherein the detecting is done by hybridizing a labeled probe (Column 22, lines 9-42).

Regarding Claim 26, Macevicz discloses the method wherein said discrete sites comprise wells (Column 32, lines 5-10).

Regarding Claim 27, Macevicz discloses the method wherein the detecting is done by hybridizing a labeled probe (Column 24, lines 63-67). And Ullman et al teach their similar method wherein the detecting is done by hybridizing a labeled probe (Column 22, lines 9-42).

Response to Arguments

6. Applicant argues that the suggestion to combine the teachings provided in the above rejection fails to point to a suggestion for making the specific modification of immobilizing both target and primer as claimed. The argument has been considered but is not found persuasive. Applicant appears to be asserting the instant claims require concurrent immobilization of target and primer. However, the claims are not so limited. While the claims do require immobilization of the target and in subsequent steps immobilization of the primer for detection of the primer. Hence, the final immobilization for improved detection as discussed above provides the needed suggestion.

Applicant asserts that each of the cited references describe satisfactory results using their methods, none of the references teach all the elements of the claimed invention and none of the references suggest modifications. For these reasons, Applicant asserts one of ordinary skill in the art would not have been motivated to modify their teachings to obtain the claimed invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as discussed above, Collins clearly provides a motivation for immobilizing the product as a final step prior to detection.

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7. Claims 18 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Macevicz (U.S. Patent No. 6,280,935, filed 4 June 1998) in view of Ullman et al (U.S. Patent No. 5,185,243, issued 9 February 1993) and Collins (U.S. Patent No. 5,750,338, issued 12 May 1998) as applied to Claims 29 and 22 above and further in view of Walt et al (U.S. Patent No. 6,327,410, filed 11 September 1998).

Regarding Claims 18 and 25, Macevicz teaches a method of detecting a target nucleic acid sequence and a library of targets, said method comprising: hybridizing a first primer portion comprising an adapter sequence (ligation probe) to a target sequence; hybridizing a second primer to a second portion of said target sequence; ligating said first and second primer to form a modified primer; contacting said modified primer with an array comprising: a substrate with a surface comprising discrete sites and a population of microspheres comprising a first nucleic acid capture probe that hybridizes to said adapter sequence wherein said microspheres are distributed on said surface and detecting the presence of said target sequence (Column 34, lines 11-38). And Ullman et al teach a similar method comprising: wherein the first and second target regions are not adjacent; extending one of the primer toward the other and ligating said first and second primer to form a modified primer and capturing the modified primer (Column 4, line 45-Column 6, line 5; and Column 9, line 59-Column 10, line 18) wherein the extension of non-adjacent primers eliminates the need to identify the diagnostic sequence thereby facilitating diagnostic detection and increasing the specificity and sensitivity of diagnostic detection (Column 4, lines 3-12).

Macevicz further teaches the substrate is selected from one of many known in the art and is selected based on efficiency and optical properties (Column 14, line 61-Column 15, line 23, especially lines 17-21) but they do not specifically teach the support is a fiber optic bundle. However, Walt et al teach a similar method of target detection comprising contacting a modified target sequence with an array comprising a substrate with a patterned surface comprising discrete sites and a population of microspheres comprising a first and second subpopulation

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capture probe wherein the microspheres are distributed on said patterned surface and detecting the presence of said first modified target sequence wherein said target is labeled prior to contacting (Column 21, lines 17-25) wherein they specifically teach that their fiber optic bundle support, in addition to providing optical properties which permit optical resolution of tens of thousands of target sequences, is efficient and inexpensive (Column 4, lines 35-58 and Column 5, lines 24-30). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the fiber optic support of Walt et al to the support of Macevicz based on the suggestion of Macevicz to apply known supports based on efficiency and optical properties (Column 14, line 61-Column 15, line 23, especially lines 17-21) and for the expected benefits of exceptional efficiency and optical properties as taught by Walt et al (Column 4, lines 35-58 and Column 5, lines 24-30).

Response to Arguments

8. Applicant relies on the arguments provided for base Claims 22 and 29. The arguments have been considered and are not found persuasive as discussed above.

9. Claims 15-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barany et al. (U.S. Patent No. 6,027,889, filed 28 May 1997) in view of Ullman et al (U.S. Patent No. 5,185,243, issued 9 February 1993), Collins (U.S. Patent No. 5,750,338, issued 12 May 1998). and Walt et al. (U.S. Patent No. 6,023,540, filed 14 May 1997).

Regarding Claim 29, Barany et al. teach a method of detecting a target nucleic acid sequence comprising: hybridizing a first primer to a first portion of a target sequence wherein said first primer further comprises an adapter sequence; hybridizing a second primer to a second portion of said target sequence; ligating said first and second primers to form a

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modified primer; contacting said adapter sequence of said modified primer with an array comprising: a substrate with a surface comprising discrete sites comprising at least a first sub-population comprising a first capture probe, such that said first capture probe and said modified first target nucleic acid sequence form a hybridization complex; and detecting the presence of said modified first target nucleic acid sequence (Column 26, line 37-Column 27, line 19 and Claim 13). The extra method steps of Barany et al. are encompassed by the open claim language "comprising" of the instant claims.

Barany et al. do not teach the method wherein the primers are not adjacent. However, Ullman et al teach a similar method comprising: wherein the first and second target regions are not adjacent; extending one of the primer toward the other and ligating said first and second primer to form a modified primer and capturing the modified primer (Column 4, line 45-Column 6, line 5; and Column 9, line 59-Column 10, line 18) wherein the extension of non-adjacent primers eliminates the need to identify the diagnostic sequence thereby facilitating diagnostic detection and increasing the specificity and sensitivity of diagnostic detection (Column 4, lines 3-12). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the primers of Barany et al by designing primers that hybridize to non-adjacent target positions as taught by Ullman et al for the expected benefit of eliminating the need to identify the diagnostic sequence thereby facilitating diagnostic detection and further increasing the specificity and sensitivity of diagnostic detection as taught by Ullman et al (Column 4, lines 3-12).

Barany et al. do not teach the method wherein the array further comprises a population of microspheres comprising the at least first sub-population wherein said microspheres are distributed on said surface. However, Walt et al. teach a similar method for detecting a target nucleic acid sequence comprising: contacting said first target nucleic acid sequence with an array comprising: a substrate with a patterned surface comprising discrete sites; and a population of microspheres comprising at least a first sub-population comprising a first

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capture probe such that said first capture probe and said first target nucleic acid sequence form a hybridization complex, wherein said microspheres are distributed on said surface (Column 4, lines 4-14); and detecting the presence of said first target nucleic acid sequence (Column 10, lines 4-41) wherein microspheres comprising different capture probes are mixed but individually detected and identified allowing for individual identification of thousands of captured target sequences using an apparatus which is easy to manufacture and use (Column 3, lines 17-30). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the array of Barany et al. to further comprise microspheres wherein the microsphere are distributed on the array at discrete site and wherein the microspheres comprise the capture probes for the expected benefit of individual identification of thousands of captured target sequences using an apparatus which is easy to manufacture and use as taught by Walt et al. (Column 3, lines 17-30).

Barany, Walt and Ullman do not teach the target is immobilized on a solid phase surface during hybridization between the first primer and target. However, target immobilization during a first hybridization step was well known in the art at the time the claimed invention was made as taught by Collins (e.g. Fig.6). Collins et al teach a similar method of target detection comprising a first step of hybridizing a first primer and a target, wherein the target is immobilized whereby the target immobilization facilitates removal of non-specific material from the sample and concentrates the target for detection and greater purification of detectable product (Column 5, lines 19-25). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the target immobilization of Collins et al to the target detection of Barany, Walt and Ullman for the expected benefit removal of non-specific material from the sample, concentration the target for detection and greater purification of detectable product as taught by Collins (Column 5, lines 19-25).

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Regarding Claim 15, Barany et al. teach the method further comprising detecting a second target sequence (i.e. array) thereby comprising hybridizing third and forth primers to first and second portions of the second target; contacting with said array and detecting the presence of said second target (Fig. 9).

Regarding Claim 16, Barany et al. teach the method wherein the modified primer is amplified (Column 27, lines 1-2).

Regarding Claim 17, Barany et al. teach the method wherein said the detecting is done by hybridizing a labeled probe to the ligated primers (Column 33, lines 16-39).

Regarding Claim 18, Barany et al. teach the substrate is an array (Column 27, lines 10-15) but they do not teach the array is a fiber optic bundle. However, Walt et al. teach the similar method wherein the substrate is a fiber optic bundle (Column 4, lines 4-14). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the array of Barany et al. to further comprise microspheres wherein the microsphere are distributed on a fiber optic bindle substrate for the expected benefit of individual identification of thousands of captured target sequences using an apparatus which is easy to manufacture and use as taught by Walt et al. (Column 3, lines 17-30).

Regarding Claim 19, Barany et al. teach said substrate comprises discrete sites (Column 27, lines 10-15) but they do not teach said discrete sites comprise wells. However, Walt et al. teach the similar method wherein said discrete sites comprise wells (Column 4, lines 4-14). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the discrete sites on the substrate of Barany et al. to provide microspheres distributed on a substrate at the discrete sites and wherein each discrete site comprises a well for the expected benefit of individual identification of thousands of captured target sequences using an apparatus which is easy to manufacture and use as taught by Walt et al. (Column 3, lines 17-30).

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Regarding Claim 20, Barany et al teach the method wherein the detecting is done by labeling amplification products (Column 27, lines 2-19).

Regarding Claim 21, Barany et al teach the method wherein one of the primers is allele specific (Column 25, lines 1-25).

Regarding Claim 22, Barany et al. teach a method of detecting at least sixteen target nucleic acids (i.e. an array, Fig. 9) sequence comprising: hybridizing a first primer to a first portion of a target sequence wherein said first primer further comprises an adapter sequence; hybridizing a second primer to a second portion of said target sequence; ligating said first and second primers to form a modified primer; contacting said adapter sequence of said modified primer with an array comprising: a substrate with a surface comprising discrete sites comprising at least a first sub-population comprising a first capture probe, such that said first capture probe and said modified first target nucleic acid sequence form a hybridization complex; and detecting the presence of said modified first target nucleic acid sequence (Fig. 15, Column 26, line 37-Column 27, line 19 and Claim 13). The extra method steps of Barany et al. are encompassed by the open claim language "comprising" of the instant claims.

Barany et al. do not teach the method wherein the primers are extended toward each other. However, Ullman et al teach a similar method comprising: extending one primer toward the other and ligating said first and second primer to form a modified primer and capturing the modified primer (Column 4, line 45-Column 6, line 5; and Column 9, line 59-Column 10, line 18) wherein the extension of non-adjacent primers eliminates the need to identify the diagnostic sequence thereby facilitating diagnostic detection and increasing the specificity and sensitivity of diagnostic detection (Column 4, lines 3-12). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the primers of Barany et al by designing primers that hybridize to non-adjacent target positions as taught by Ullman et al for the expected benefit of eliminating the need to identify the diagnostic sequence

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thereby facilitating diagnostic detection and further increasing the specificity and sensitivity of diagnostic detection as taught by Ullman et al (Column 4, lines 3-12).

Barany et al. do not teach the method wherein the array further comprises a population of microspheres comprising the at least first sub-population wherein said microspheres are distributed on said surface. However, Walt et al. teach a similar method for detecting a target nucleic acid sequence comprising: contacting said first target nucleic acid sequence with an array comprising: a substrate with a patterned surface comprising discrete sites; and a population of microspheres comprising at least a first sub-population comprising a first capture probe such that said first capture probe and said first target nucleic acid sequence form a hybridization complex, wherein said microspheres are distributed on said surface (Column 4, lines 4-14); and detecting the presence of said first target nucleic acid sequence (Column 10, lines 4-41) wherein microspheres comprising different capture probes are mixed but individually detected and identified allowing for individual identification of thousands of captured target sequences using an apparatus which is easy to manufacture and use (Column 3, lines 17-30). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the array of Barany et al. to further comprise microspheres wherein the microsphere are distributed on the array at discrete site and wherein the microspheres comprise the capture probes for the expected benefit of individual identification of thousands of captured target sequences using an apparatus which is easy to manufacture and use as taught by Walt et al. (Column 3, lines 17-30).

Barany, Walt and Ullman do not teach the target is immobilized on a solid phase surface during hybridization between the first primer and target. However, target immobilization during a first hybridization step was well known in the art at the time the claimed invention was made as taught by Collins (e.g. Fig.6). Collins et al teach a similar method of target detection comprising a first step of hybridizing a first primer and a target, wherein the target is immobilized whereby the target immobilization facilitates removal of non-

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specific material from the sample and concentrates the target for detection and greater purification of detectable product (Column 5, lines 19-25). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the target immobilization of Collins et al. to the target detection of Barany, Walt and Ullman for the expected benefit removal of non-specific material from the sample, concentration the target for detection and greater purification of detectable product as taught by Collins (Column 5, lines 19-25).

Regarding Claim 23, Barany et al. teach the method wherein the modified primer is amplified (Column 27, lines 1-2).

Regarding Claim 24, Barany et al. teach the method wherein said the detecting is done by hybridizing a labeled probe to the ligated primers (Column 33, lines 16-39).

Regarding Claim 25, Barany et al. teach the substrate is an array (Column 27, lines 10-15) but they do not teach the array is a fiber optic bundle. However, Walt et al. teach the similar method wherein the substrate is a fiber optic bundle (Column 4, lines 4-14). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the array of Barany et al. to further comprise microspheres wherein the microsphere are distributed on a fiber optic bundle substrate for the expected benefit of individual identification of thousands of captured target sequences using an apparatus which is easy to manufacture and use as taught by Walt et al. (Column 3, lines 17-30).

Regarding Claim 26, Barany et al. teach said substrate comprises discrete sites (Column 27, lines 10-15) but they do not teach said discrete sites comprise wells. However, Walt et al. teach the similar method wherein said discrete sites comprise wells (Column 4, lines 4-14). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the discrete sites on the substrate of Barany et al. to provide microspheres distributed on a substrate at the discrete sites and wherein each discrete site comprises a well for the expected benefit of individual identification of thousands of captured

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target sequences using an apparatus which is easy to manufacture and use as taught by Walt et al. (Column 3, lines 17-30).

Regarding Claim 27, Barany et al teach the method wherein the detecting is done by labeling amplification products (Column 27, lines 2-19).

Regarding Claim 28, Barany et al teach the method wherein one of the primers is allele specific (Column 25, lines 1-25).

Response to Arguments

10. Applicant argues that the suggestion to combine the teachings provided in the above rejection fails to point to a suggestion for making the specific modification of immobilizing both target and primer as claimed. The argument has been considered but is not found persuasive. Applicant appears to be asserting the instant claims require concurrent immobilization of target and primer. However, the claims are not so limited. While the claims do require immobilization of the target and in subsequent steps immobilization of the primer for detection of the primer. Hence, the final immobilization for improved detection as discussed above provides the needed suggestion.

Applicant asserts that each of the cited references describe satisfactory results using their methods, none of the references teach all the elements of the claimed invention and none of the references suggest modifications. For these reasons, Applicant asserts one of ordinary skill in the art would not have been motivated to modify their teachings to obtain the claimed invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071,

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5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as discussed above, Collins clearly provides a motivation for immobilizing the product as a final step prior to detection.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 15-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 and 27-32 of U.S. Patent No. 6,355,431. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to very similar methods for detecting target sequences and differ only in the arrangement of limitations within the claims sets. For example, independent Claims 22 and 29 of the instant invention recite primer extension and ligation steps. In slight contrast, various dependent claims (e.g. 5-6, 12) define the method as comprising primer extension and/or ligation. As such, the instant claims are an obvious variation of the patent claims.

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13. Claims 15-29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-31, 42-44, 46, 48 and 50-52 of copending Application No. 09/425,633. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to similar methods of detecting a target and differ only in the '633 claims being drawn to nucleotide target while the instant claims are drawn to a nucleic acid sequence target. However, both sets of claims contain very similar method steps concluding with target detection via detection of ligated product. The '633 nucleotide target is considered a species of the instantly claimed nucleic acid sequence target because the instantly claimed sequence comprise target nucleotides.

The courts have stated that a genus is obvious in view of the teaching of a species see Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); and In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989).

For all the reasons stated above, the instantly claimed methods are obvious in view of the '633 methods.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Remarks

14. On page 17 of the Response, Applicant requests to defer the time for responding to the above rejections under obviousness-type double patenting. The request is noted. However, it is not Office policy to defer response time. The time for response is not deferred. The rejection is maintained and made FINAL.

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Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (571) 272-0741. The examiner can normally be reached on 6:00 TO 3:30.

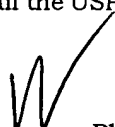
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.


BJ Forman, Ph.D.
Primary Examiner
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March 23, 2005